IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/531,160
Cnfrm. No.	:	4722
Applicant	:	Boris Shekunov et al.
Filed	:	April 12, 2005
Title	:	NANOPARTICLES FROM SUPERCRITICAL FLUID ANTISOLVENT PROCESS USING PARTICLE GROWTH AND AGGLOMERATION RETARDANTS
TC/A.U.	:	1618
Examiner	:	Nabila G. Ebrahim
Docket No.	:	FER-14857.001.001

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This Appeal Brief is being filed in accordance with 37 C.F.R. §41.37 within two months of the Notice of Appeal that was filed in this matter on October 25, 2007.

I. REAL PARTY IN INTEREST

The real party in interest or owner of the present application and the technology and inventions embodied therein is Ferro Corporation, whose principal mailing address is 1000 Lakeside Avenue, Cleveland, Ohio 44114. An assignment transferring rights from the inventors to Ferro Corporation was recorded on April 12, 2005 at Reel 017179, Frame 0141.

II. RELATED APPEALS AND INTERFERENCES

The application is not involved in an interference proceeding and there are no related appeals.

III. STATUS OF CLAIMS

The application was filed on April 12, 2005 with 21 claims. On March 31, 2006, the Examiner issued a first Office Action in which he rejected all 21 claims on various grounds.

On April 18, 2006, applicants filed their first Amendment, which amended claims 4, 11 and 18 to correct a typographical error. On June 29, 2006, the Examiner issued a second Office Action in which he repeated the prior rejection of all 21 claims and made the rejection thereof final.

Applicants filed their first Notice of Appeal on September 15, 2006 and submitted their first Appeal Brief on October 23, 2006. In a third Office Action mailed on February 9, 2007, the Examiner withdrew the finality of the second Office Action dated June 29, 2006 and rejected claims 1-21 on different grounds.

On May 7, 2007, applicants filed their second amendment, which canceled claims 8-14. On July 26, 2007, the Examiner issued a fourth Office Action in which he repeated the prior rejection of claims 1-7 and 15-21 and made the rejection thereof final.

Applicants filed their second Notice of Appeal on October 25, 2007. Claims 1-7 and 15-21 are pending in the application. The pending claims are set forth in the Claims Appendix, which is attached hereto for the convenience of the Board.

IV. STATUS OF AMENDMENTS

No amendments were filed in the application subsequent to the final rejection mailed on July 26, 2007.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The application claims methods of forming small, in most cases nanometer-sized, solid particles using a supercritical fluid ("SCF") and one or more particle growth and agglomeration retardant compounds. The application contains two independent claims, namely claims 1 and 15. Dependent claims 2-7 and 16-21 depend from independent claims 1 and 15, respectively, and are grouped for purposes of this appeal.

Claim 1 claims a method whereby the one or more particle growth and agglomeration retardant compounds are present in a solution that includes a solute dissolved in a solvent. The solution contacts the SCF. Because the solvent in the solution is soluble in the SCF, the

concentration of the solvent in the solution rapidly decreases when the solution contacts the SCF thereby causing supersaturation and subsequent precipitation of the solute as solid particles. Thus, the method claimed in claim 1 modifies the prior art Supercritical fluid Anti-Solvent (SAS) process by including one or more particle growth and agglomeration retardant compounds in the solution that contacts the SCF.

Claim 15 claims a method whereby the one or more particle growth and agglomeration retardant compounds are dissolved in the SCF with a solute to form an SCF solution. The SCF solution is then expanded across a pressure drop, which causes the SCF to change phase and become gaseous. Because the SCF is changing phase to become a gas, the concentration of SCF in the SCF solution rapidly decreases thereby causing supersaturation and subsequent precipitation of the solute as solid particles. Thus, the method claimed in claim 15 modifies the prior art Rapid Expansion of Supercritical fluid Solvent (RESS) process by including one or more particle growth and agglomeration retardant compounds in the SCF solution.

In both of the claimed methods, the one or more growth and agglomeration retardant compounds hinder nuclei coalescence, which results in the precipitation of smaller particles that would otherwise be obtained. In addition, the one or more growth and agglomeration retardant compounds also hinder particle interaction after precipitation, which minimizes particle agglomeration.

Claim 1 is set forth below with references to the specification by page and line number and to the drawing figures enclosed in brackets:

> A method of producing particles using supercritical fluid (SCF) comprising [see, generally, page 10, line 27 to page 12, line 13 and Fig. 1]:
>
> providing a source of SCF [see page 10, lines 5-10];
>
> providing a solution comprising [see page 9, lines 7-9]:
>
> at least one solvent that is at least partially soluble in the SCF [see page 9, line 10];
>
> at least one solute material that is at least partially soluble in the solvent [see page 9, lines 13-14], and substantially insoluble in the SCF [see page 10, lines 13-14]; and

at least one growth retardant compound that is at least partially soluble in the SCF and includes at least one functional group or portion that is SCF-philic and at least one functional group or portion that is SCF-phobic or solute material-philic [see page 7, lines 7-10; and page 6, lines 7-10]; and

contacting the solution and the SCF together under conditions whereby the solvent diffuses into the SCF causing supersaturation and nucleation of particles comprising the solute material [see page 11, lines 12-16], said particles having a smaller size and a reduced amount of agglomeration than if no growth retardant compound was present [see page 7, 24-27].

Claim 15 is set forth below with references to the specification by page and line number and to the drawing figures enclosed in brackets:

A method of producing particles using supercritical fluid (SCF) comprising [see, generally, page 13, line 28 to page 15, line 29 and Fig. 3]:

providing a source of SCF [see page 10, lines 5-10];

dissolving at least one solute material and at least one growth retardant compound in the SCF to form an SCF solution [see page 6, lines 11-13], wherein the growth retardant compound includes at least one functional group or portion that is SCF-philic and at least one functional group or portion that is SCF-phobic or solute material-philic [see page 7, lines 7-10]; and

expanding SCF solution across a pressure drop below the critical pressure of the SCF whereby the SCF decompresses and causes supersaturation and nucleation of particles comprising the solute material [see page 7, lines 14-17], said particles having a smaller size and a reduced amount of agglomeration than if no growth retardant compound was present [see page 7, 24-27].

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1-7 (Grouped) and claims 15-21 (Grouped) were properly rejected under 35 U.S.C. §103(a) as being unpatentable over Subramaniam et al., U.S. Pat. 5,874,029, in view of Henriksen et al., U.S. Pat. 6,974,593.

VII. ARGUMENT

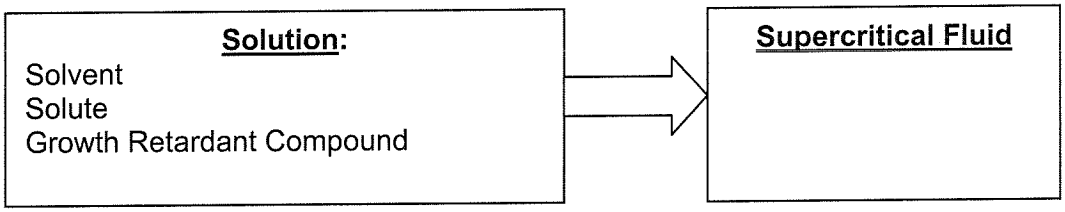
A. Claims 1-7 (Grouped) Were Improperly Rejected Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-7 under 35 U.S.C. §103(a) as being unpatentable over Subramaniam et al., U.S. Pat. 5,874,029, in view of Henriksen et al., U.S. Pat. 6,974,593. For the reasons set forth below, applicants respectfully submit that the Examiner's rejection of such claims was improper, and should be reversed.

In accordance with the invention as claimed in claim 1:

- a solution comprising a solvent, a solute and a growth retardant compound is provided;
- a supercritical fluid is provided; and
- the solution and the supercritical fluid are contacted together.

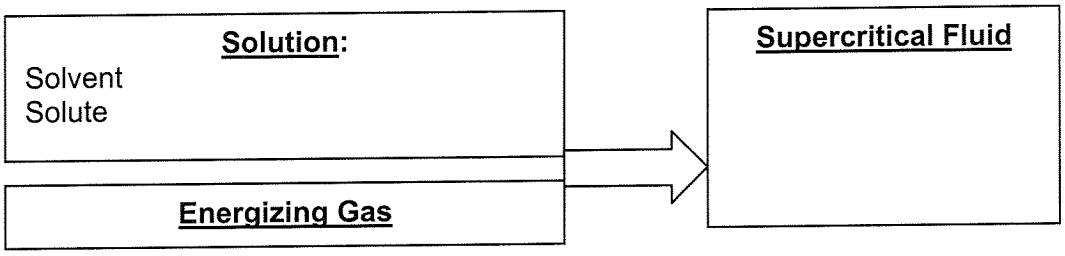
The method as claimed in claim 1 is graphically depicted below:



Upon contacting the SCF, the concentration of the solvent, which is soluble in the SCF, rapidly decreases causing supersaturation and subsequent precipitation of the solute as solid particles.

Subruamaniam et al. discloses a method for producing particles using supercritical fluid. However, the method according to Subrumaniam et al. is significantly different from the method claimed in claim 1. Subrumaniam et al. teaches that a solution comprising a solvent and a dissolved solute material should sprayed out of a nozzle in the form of atomized droplets into a supercritical fluid antisolvent, which causes depletion of the solvent in the atomized droplets of solution and recrystallization of the solute in the form of particles. This is very similar to the prior art SAS process, with one exception. Subramaniam et al. teaches that the solution should be introduced into the nozzle together with an "energizing gas" (which Subrumaniam et al. also refers to as a "compressed fluid" or "compressed gas" - see col. 8, lines 9-10), which exits the

nozzle at a velocity such that the spray of solution into the SCF is "shattered into extremely small droplets at the nozzle exit" (col. 6, line 1-8). Thus, the method according to Subrumaniam et al. can be graphically depicted as follows:



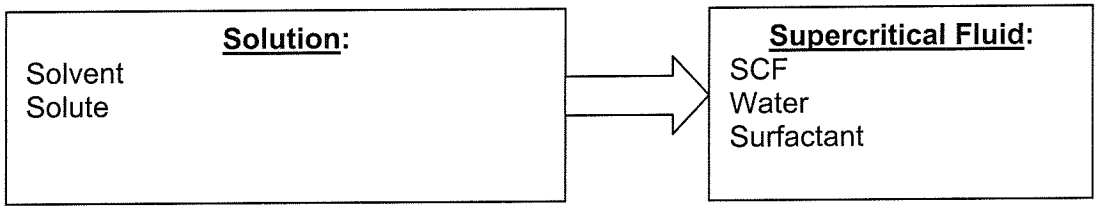
Subrumaniam et al. does not ever disclose, teach or suggest that a growth retardant compound should be mixed into the solution before the solution and the supercritical fluid are contacted together. And this makes perfect sense considering that Subramaniam et al.'s solves the problem of obtaining small particles by using an energizing gas to blast the solution into small particles, and not by including a growth retardant compound (which the claims define as a compound that is at least partially soluble in the SCF and includes at least one functional group or portion that is SCF-philic and at least one functional group or portion that is SCF-phobic or solute material-philic) into the solution that contacts the SCF. The Examiner disregards this difference.

In prior Office Actions, the Examiner made reference to claim 3 of the present application, which specifies that the growth retardant compounds can be selected from "fluorocarbons". The Examiner noted that Subrumaniam et al. mentions trifluoromethane ("CHF_3"), which is a fluorocarbon, apparently concluding that the use of trifluoromethane ("CHF_3") would anticipate or render applicants claimed invention obvious. However, when applicants pointed out to the Examiner that Subramaniam et al. mentioned trifluoromethane ("CHF_3") once, and only in the context of trifluoromethane ("CHF_3") being suitable for use as an SCF antisolvent (i.e., the material into which the solution is atomized, and not as a constituent of the solution), the Examiner stated that he did not find this persuasive. The Examiner did not explain why one having ordinary skill in the art would be motivated by Subramaniam et al.'s teaching that trifluoromethane ("CHF_3") can be used as a SCF to add trifluoromethane ("CHF_3") to a solution that is contacted with a SCF.

Applicants contend that in order for Subramaniam et al. to be pertinent to the invention as claimed in claim 1, Subrumaniam et al. would have to teach that a compound that is at least partially soluble in the SCF and includes at least one functional group or portion that is SCF-

philic and at least one functional group or portion that is SCF-phobic or solute material-philic should be used as a constituent of the solution that contacts the supercritical fluid antisolvent. Subrumaniam et al. simply does not teach this. And neither does the other prior art reference of record, namely Henriksen et al.

Henriksen et al. teaches methods for producing aqueous suspensions of water-insoluble drugs (see col. 6, lines 19-21) using either a modified RESS process or SAS process. In the SAS process according to Henriksen et al., a water insoluble drug is dissolved in a suitable organic solvent. The water insoluble drug would constitute a solute. The resulting solution is then contacted with a supercritical fluid antisolvent mixture comprising a supercritical fluid, water and a surfactant. The solvent in the solution is taken up by the supercritical fluid antisolvent, causing the solute to precipitate into the aqueous surfactant and thereby form an aqueous suspension of solute particles. The supercritical antisolvent process according to Henriksen can thus be graphically depicted as follows:



First off, there is clearly no reason one skilled in the art would combine the teachings of Henriksen et al. with Subrumaniam et al. Both accomplish the same goal (the precipitation of particles having a smaller size), but they accomplish this goal using different means. Subramaniam et al. does it through the use of an energizing gas that blasts the solution into small droplets. Henriksen does it by including a surfactant in the SCF solution. Nevertheless, even if one were motivated by the teachings of Henriksen et al. to modify Subrumaniam et al. to include water and a surfactant in the supercritical fluid antisolvent, such combination would not read on applicants' invention as claimed in claim 1, which requires that the growth retardant compound (which is similar to the surfactant in Henriksen et al.) be dissolved as part of the solution that is contacted together with the supercritical fluid. In other words, combining Henriksen et al. with Subrumaniam et al. produces a process where the surfactant is in the wrong spot (i.e., it is mixed with the supercritical fluid and water rather than being present in the solution that is contacted with the supercritical fluid). Thus, the applied references, even when combined, clearly do not read on applicants' method as claimed in claim 1.

The Examiner has failed to demonstrate why one having ordinary skill in the art would be

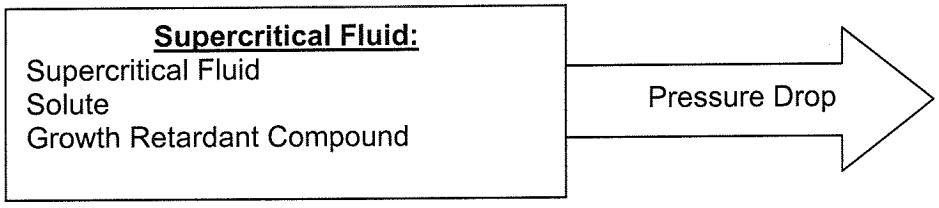
motivated to include a growth retardant compound in the solution that contacts the SCF, or why one would reasonably expect a benefit to be obtained by doing so.

In *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (2007), the Court noted that the now-rejected teaching-suggestion-motivation (TSM) rationale could still be relied upon to reject a claim under 35 U.S.C. §103(a), where appropriate. Applicants note that the TSM test cannot be used in the present case to reject claim 1 because there is no teaching, suggestion or motivation in the applied references to include a particle growth retardant compound in the solution that contacts the SCF. Neither of the prior art references relied upon by the Examiner fairly teach this. Applicants respectfully submit that further consideration of the *Graham* factors further prove that applicants' invention as claimed in claim 1 is not obvious.

The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court (quoting *In re Kahn*, 441 F.3d 977 (Fed. Cir. 2006)), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'". The Examiner has not set forth any basis for concluding that a person of ordinary skill in the art would find it obvious to add a growth retardant compound to a solution to modify the SAS process as applicants claim in claim 1. There is nothing that suggests that the results from doing so would be predictable. The rejection is simply unsupported by the record, and should be reversed.

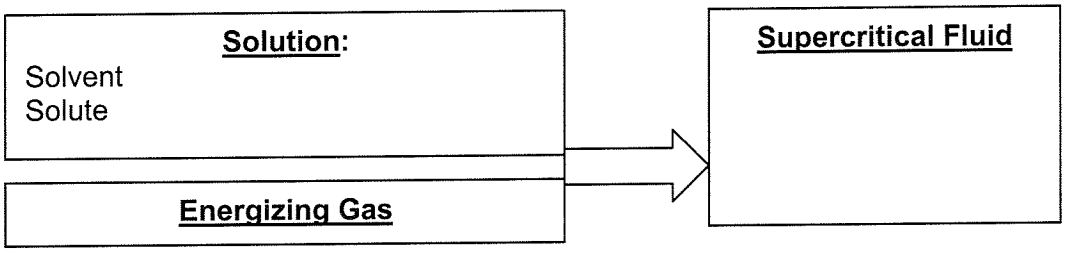
B. Claims 15-21 (Grouped) Were Improperly Rejected Under 35 U.S.C. §103(a)

In accordance with the invention as claimed in claim 15, a solute and a growth retardant compound are dissolved in a supercritical fluid, which is then expanded across a pressure drop to produce particles, as graphically depicted below:

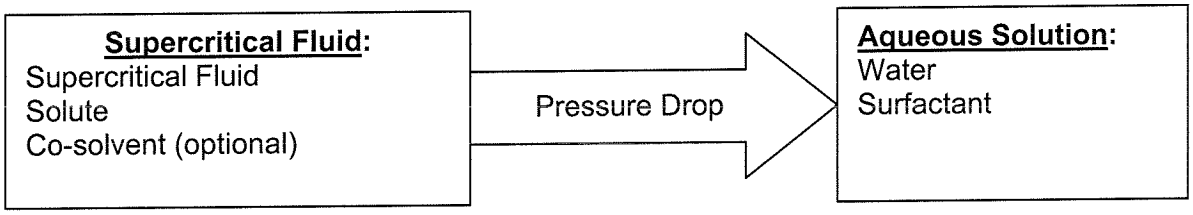


Subrumaniam et al. does not teach a process whereby a supercritical fluid is rapidly expanded across a pressure drop (i.e., an RESS process). On the contrary, Subrumaniam et al. discloses a modified SAS process whereby a solution of a solute dissolved in a solvent is

sprayed through a nozzle simultaneously with an energizing gas into a volume containing a supercritical fluid, which acts as an antisolvent for the solvent and thereby causes the recrystallization of the solute as particles. As noted above, Subrumaniam et al. can be graphically depicted as follows:



In one embodiment, Henriksen et al. does teach a modified RESS process. In that embodiment of the invention, Henriksen et al. teaches that a water insoluble drug should be dissolved in a supercritical fluid (optionally in the presence of a co-solvent) and expanded across a pressure drop and into an aqueous solution containing a surfactant. The modified RESS embodiment of Henriksen et al. can be graphically depicted as follows:



Henriksen et al. clearly does not disclose the same invention as claimed in claim 15. The "surfactant", to the extent it would constitute a growth retardant compound as claimed, is not in the right place. It is on the other side of the pressure drop and mixed with water. It is not dissolved in the SCF solution before it is pumped across the pressure drop.

Henriksen et al. cannot be combined with Subramaniam et al. in such a way as to lead to applicants' invention as claimed in claim 15. As noted above, Subramaniam et al. discloses a modified SAS process, not a modified RESS process. There is no way to combine the two processes. One employs SCF as an antisolvent for a solvent in a solution that is pumped into the SCF. The other employs SCF as a solvent for a solute, and rapidly expands the SCF to precipitate particles of the solute.

The Examiner does not explain why or how a person having ordinary skill in the art would modify Henriksen et al. to arrive at applicants' invention as claimed in claim 15. The Examiner has not set forth any basis for concluding that a person of ordinary skill in the art

would find it obvious to add a growth retardant compound to an SCF solution to modify the RESS process as applicants claim in claim 15. There is nothing that suggests that the results from doing so would be predictable. The rejection is simply unsupported by the record, and should be reversed.

C. Provisional Double-Patenting Rejections

Applicants note that in the prior Office Action, the Examiner provisionally rejected claims 1-21 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9-13, 15 and 16 of then copending application No/ 10/534,665 (now U.S. Pat. 7,279,181) and co-pending application No. 10/789,422. Applicants reserve the right to file terminal disclaimers to obviate the double-patenting rejections subsequent to a Decision on this appeal.

Conclusion

In view of the foregoing, it is respectfully submitted that claims 1-7 and 15-21 are allowable over the prior art references of record, and a ruling from the Board to that effect is therefore respectfully requested.

Respectfully submitted,

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CLAIMS APPENDIX

Claim 1 (original): A method of producing particles using supercritical fluid (SCF) comprising:

providing a source of SCF;

providing a solution comprising:

at least one solvent that is at least partially soluble in the SCF;

at least one solute material that is at least partially soluble in the solvent and substantially insoluble in the SCF; and

at least one growth retardant compound that is at least partially soluble in the SCF and includes at least one functional group or portion that is SCF-philic and at least one functional group or portion that is SCF-phobic or solute material-philic; and

contacting the solution and the SCF together under conditions whereby the solvent diffuses into the SCF causing supersaturation and nucleation of particles comprising the solute material, said particles having a smaller size and a reduced amount of agglomeration than if no growth retardant compound was present.

Claim 2 (original): The method according to claim 1 wherein the SCF is supercritical carbon dioxide.

Claim 3 (original): The method according to claim 2 wherein the growth retardant compound is selected from the group consisting of sugar acetates, fluorocarbons and block copolymers.

Claim 4 (previously presented): The method according to claim 2 wherein the block copolymer is comprised of polymer blocks selected from the group consisting of polypropylene oxide, poly methacrylic acid (PMMA), poly acrylic acid (PAA), poly vinyl acetate (PVA) and polyethylene oxide (PEO).

Claim 5 (original): The method according to claim 1 wherein the solute material is selected from the group consisting of medicinal agents, biologically active materials, sugars, viral materials, diagnostic aids, nutritional materials, proteins, peptides, animal extracts, plant extracts and combinations thereof.

Claim 6 (original): The method according to claim 5 wherein the solution further comprises a second solute material selected from the group consisting of polymers, fillers, disintegrants, binders, solubilizers, excipients, and combinations thereof. In particular, the matrix materials can be, for example, polysaccharides, polyesters, polyethers, polyanhydrides, polyglycolides (PLGA), polylactic acids (PLA), polycaprolactones (PCL), polyethylene glycols (PEG), polypeptides and combinations thereof.

Claim 7 (original): The method according to claim 6 wherein the particles have an average particle size of less than 10 micron and more than 300 nm.

Claims 8-14 (canceled)

Claim 15 (original): A method of producing particles using supercritical fluid (SCF) comprising:

providing a source of SCF;

dissolving at least one solute material and at least one growth retardant compound in the SCF to form an SCF solution, wherein the growth retardant compound includes at least one functional group or portion that is SCF-philic and at least one functional group or portion that is SCF-phobic or solute material-philic; and

expanding SCF solution across a pressure drop below the critical pressure of the SCF whereby the SCF decompresses and causes supersaturation and nucleation of particles comprising the solute material, said particles having a smaller size and a reduced amount of agglomeration than if no growth retardant compound was present.

Claim 16 (original): The method according to claim 15 wherein the SCF is supercritical carbon dioxide.

Claim 17 (original): The method according to claim 16 wherein the growth retardant compound is selected from the group consisting of sugar acetates, fluorocarbons and block copolymers.

Claim 18 (previously presented): The method according to claim 17 wherein the block copolymer is comprised of polymer blocks selected from the group consisting of polypropylene oxide, poly methacrylic acid (PMMA), poly acrylic acid (PAA), poly vinyl acetate (PVA) and polyethylene oxide (PEO).

Claim 19 (original): The method according to claim 15 wherein the solute material is selected from the group consisting of medicinal agents, biologically active materials, sugars, viral materials, diagnostic aids, nutritional materials, proteins, peptides, animal extracts, plant extracts and combinations thereof.

Claim 20 (original): The method according to claim 19 wherein the solution further comprises a second solute material selected from the group consisting of polymers, fillers, disintegrants, binders, solubilizers, excipients, and combinations thereof. In particular, the matrix materials can be, for example, polysaccharides, polyesters, polyethers, polyanhydrides, polyglycolides (PLGA), polylactic acids (PLA), polycaprolactones (PCL), polyethylene glycols (PEG), polypeptides and combinations thereof.

Claim 21 (original): The method according to claim 20 wherein the particles have an average particle size of less than 10 micron and more than 300 nm.

EVIDENCE APPENDIX

No evidence was submitted by the applicants pursuant to 37 C.F.R. §1.130, 1.131 or 1.132, and no evidence was entered by the Examiner and relied upon by the applicants in this appeal.

RELATED PROCEEDINGS APPENDIX

There are no related proceedings.